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Original Article

# Sleep duration and the risk of future lipid profile abnormalities in middle-aged men: the Kansai Healthcare Study

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ABSTRACT

*Background:* Although short sleep duration has been reported to be associated with future cardiometabolic diseases, it is not fully understood whether sleep duration is prospectively associated with the risk of each lipid profile abnormality.
*Methods:* Subjects were nondiabetic Japanese, 40–55 years of age, who were not taking oral lipid-lowering medications: for the incidence of low high-density lipoprotein cholesterol (HDL-C), 7627 men with an HDL-C level ≥40 mg/dL; for high triglycerides, 6973 men with a triglyceride level <200 mg/dL; for high low-density lipoprotein cholesterol (LDL-C), 7273 men with an LDL-C level <160 mg/dL; for high non-HDL-C, 7415 men with a non-HDL-C level <190 mg/dL; and for high total cholesterol (TC), 7196 men with a TC level <240 mg/dL. Lipid profile abnormalities were defined according to the Adult Treatment Panel III guidelines of the National Cholesterol Education Program.
*Results:* During the 6-year observation period, there were 1022 cases of low HDL-C. Multiple-adjusted hazard ratios for low HDL-C were 0.79 (95% confidence interval, 0.64–0.97) for sleep durations of 5 to <7 h and 0.62 (0.46–0.83) for ≥7 h compared with <5 h. There were 1473 cases of high triglycerides. Multiple-adjusted hazard ratios for high triglycerides were 0.81 (0.68–0.98) for sleep durations of 5 to <7 h and 0.90 (0.72–1.13) for ≥7 h compared with <5 h. However, no association between sleep duration and the risk of future high LDL-C, non-HDL-C, or TC was observed.
*Conclusions:* Moderate and/or long sleep durations decreased the risk of future low HDL-C and high triglycerides.



## 1. Introduction

In many countries, sleep duration among adults has declined. Japan shows the largest decrease in sleep duration overall, with people sleeping 2.8 h less per week in the 2000s than in the 1960s [1]. Sleep duration in Japan is shorter than in any other country [2]. Short sleep duration has been reported to be associated with the risk of mortality [3], cardiovascular events [4], obesity [5–7], diabetes mellitus [8], and hypertension [9]. However, it is not known whether sleep duration is prospectively associated with the risk of future lipid profile abnormalities.

With few exceptions, epidemiologic studies of sleep duration and dyslipidemia have been cross-sectional rather than prospective. The results in previous cross-sectional studies have been inconclusive [10–13]. For high-density lipoprotein (HDL) cholesterol, Hall et al. [10] reported a U-shaped association between sleep duration and low HDL cholesterol in 1214 subjects aged 30–55 years, although the association between shorter sleep duration and low HDL cholesterol was not statistically significant. However, Arora et al. [11] reported that, in elderly subjects aged 50–96 years, shorter self-reported sleep duration was related to a lower odds of low HDL cholesterol. Kaneita et al. [12], in the National Health and Nutrition Survey in Japan, reported no significant association between sleep duration and low HDL cholesterol. As for triglycerides, Hall et al. [10] and Kaneita et al. [12] reported that short sleep duration was associated with an increased odds of high triglycerides, but Arora et al. [11] reported that longer sleep duration was associated with an increased odds of high triglycerides. Differences in the age distribution of study subjects, incomplete control for confounding factors, or not using fasting samples to measure lipid profile levels may explain the inconclusive associations thus far. Only two prospective studies have reported the association between sleep duration and each lipid profile abnormality [14] or hypercholesterolemia [15]. These results have been conclusive. Ruiter Petrov et al. [14] reported in the Coronary Artery Risk Development in Young

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Adults Study that longer sleep duration was associated with increased future total cholesterol levels and triglyceride levels, but not with HDL cholesterol. Gangwisch et al. [15] reported in the National Longitudinal Study of Adolescent Health that longer sleep duration was associated with a decreased risk of hypercholesterolemia, but they did not examine the association between sleep duration and other lipid profiles. In prospective cohort studies, it has not been fully examined whether sleep duration is associated with the risk of each lipid profile abnormality. Therefore, the present study examined the relationship between sleep duration and the risk of each lipid profile abnormality in a 6-year prospective observational study among apparently healthy middle-aged Japanese men.

## 2. Methods

### 2.1. Kansai Healthcare Study

The Kansai Healthcare Study is an ongoing cohort investigation designed to clarify the risk factors for chronic diseases [16]. Study subjects were 9027 non-diabetic male employees of a company in the area of Kansai, Japan, aged 40–55 years, who were enrolled between 1 April 2000 and 31 March 2001 and who were not taking oral lipid-lowering medications at baseline. All employees in this company aged ≥40 years underwent detailed annual medical check-ups. The protocol of this study was reviewed and approved by the Human Subjects Review Committee at Osaka City University.

### 2.2. Data collection and measurements

The clinical examination consisted of a medical history; a physical examination; anthropometric measurements; self-administered questionnaires on lifestyle characteristics, such as sleep duration, regular leisure-time physical activity, smoking habits, and daily alcohol consumption; and measurement of fasting plasma glucose, HDL cholesterol, triglyceride, and total cholesterol levels. Trained nurses carried out all measurements. Blood samples were drawn after an overnight 12 h fast. Serum total cholesterol, HDL cholesterol, and triglyceride levels were measured using a Hitachi 7350 automatic chemistry analyzer (Hitachi Co., Ltd, Tokyo, Japan) at baseline. Non-HDL cholesterol levels were calculated as total cholesterol level minus HDL cholesterol level. Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula for those whose triglyceride levels were <400 mg/dL [17]. After resting for ~5 min in a quiet room, systolic and diastolic blood pressures were measured in a sitting position with an automatic sphygmomanometer (BP-203RV; Omron Colin, Tokyo, Japan; and Udex-super; ELK Corp., Osaka, Japan) [18]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hemoglobin A1c (HbA1c) levels were measured by high-performance liquid chromatography standardized to the Japan Diabetes Society (JDS) Committee for the Standardization of Glycohemoglobin [19], using an HA-8150 automatic glycohemoglobin analyzer (Kyoto Daiichi Kagaku, Kyoto, Japan) in the same laboratory. The conversion equation from HbA1c (JDS) to HbA1c (NGSP: National Glycohemoglobin Standardization Program) levels has been officially certified as follows: NGSP (%) = 1.02 × JDS (%) + 0.25% [19]. Follow-up examinations were annually conducted at the multicenter in the area of Kansai, Japan. Blood samples were also drawn after an overnight 12 h fast. All results of detailed medical check-ups were gathered at Kansai Health Administration Center.

The questionnaire on sleep duration included the question: "How long do you sleep daily?" The questionnaire had three possible answers: <5 h, 5 to <7 h, and ≥7 h. To validate that this question was interpreted as "sleep duration in general", not as "sleep duration last night", this was investigated in a sub-cohort of 215 subjects. First, subjects were asked "How long do you sleep daily?", followed by "Which sleep duration were you asked about, in general or last night?" Of 215 subjects, 208 (97%) answered "In general". Therefore, the questionnaire used to assess sleep duration measured "sleep duration in general".

Other lifestyle questionnaires assessing regular leisure-time physical activity, smoking habits, and daily alcohol consumption have been described in detail previously [16]. To describe briefly, regarding leisure-time physical activity, subjects were classified into two groups: regular leisure-time physical activity at least once weekly or less than once weekly. Regarding smoking habits, subjects were classified into three groups: non-smokers, past smokers, and current smokers. Questions regarding alcohol intake included the weekly frequency of alcohol consumption and the usual amount of alcohol consumed on a daily basis. Daily alcohol intake (in grams of ethanol per day) was calculated. Except for non-drinkers, subjects were classified into tertiles of daily alcohol consumption levels.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or if subjects were taking antihypertensive drugs [20]. Diabetes was defined as fasting plasma glucose level ≥126 mg/dL, HbA1c level ≥6.5%, or if subjects were taking hypoglycemic medications or insulin [21].

### 2.3. Diagnosis of each lipid profile abnormality

Each lipid profile abnormality was defined according to the Adult Treatment Panel III guidelines of the National Cholesterol Education Program [22]. Specifically, low HDL cholesterol was defined as HDL cholesterol level <40 mg/dL, high LDL cholesterol as LDL cholesterol level ≥160 mg/dL, high non-HDL cholesterol as non-HDL cholesterol level ≥190 mg/dL, high triglycerides as triglyceride level ≥200 mg/dL, and high total cholesterol as total cholesterol level ≥240 mg/dL.

### 2.4. Statistical analysis

The Cox proportional hazards model was used to estimate the hazard ratio for the incidence of each lipid profile abnormality in relation to sleep duration and baseline covariates. Follow-up of each subject was continued until the diagnosis of lipid profile abnormalities at the annual follow-up examination, or until the sixth follow-up examination conducted between 1 April 2006 and 31 March 2007, whichever came first. For all models, the adequacy of the Cox proportional hazards model was assessed. Non-linear effects of continuous independent variables were evaluated by plotting the regression coefficients against the variables [23]. Continuous independent variables in all models fulfilled this linearity assumption. The proportional hazards assumption was checked using log minus log plots for categorical independent variables and the plot of Schoenfeld residuals for continuous independent variables [24]. All independent variables in all models met the assumption. To test the presence of effect modification, each first-order interaction term between sleep duration and age, BMI, smoking habits, alcohol consumption, regular leisure-time physical activity, and hypertension was examined. There were no significant interactions between sleep duration and all independent variables in all models. Multicollinearity was assessed using the variance inflation factor [25]. There was no evidence of multicollinearity. Outliers were checked by plotting the likelihood displacement values and by plotting DFBETAs for all independent variables [24]. Outliers were not detected in any model. The 95% confidence interval was calculated for each hazard ratio. Statistical analyses were performed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA) and Stata MP, version 12.0 (Stata Corp., College Station, TX, USA).

Multiple linear regression analysis was used to model each future lipid profile level as a function of other variables in relation to sleep duration and baseline covariates. Residual analysis was conducted

**Table 1**
Baseline characteristics of study subjects according to sleep duration.

| Baseline characteristics | Total | Sleep duration (h) | | |
|---|---|---|---|---|
| | | <5 | 5 to <7 | ≥7 |
| *N* | 8766 | 647 | 7124 | 995 |
| Age (years) | 47.8 ± 4.2 | 47.3 ± 4.4 | 47.8 ± 4.2 | 48.2 ± 4.1 |
| Body mass index (kg/m$^2$) | 23.4 ± 2.9 | 23.9 ± 3.0 | 23.4 ± 2.8 | 22.8 ± 2.9 |
| Hypertension (%) | 33.8 | 31.2 | 33.9 | 34.9 |
| Fasting plasma glucose (mg/dL) | 97.8 ± 9.0 | 98.5 ± 8.9 | 97.7 ± 9.0 | 97.8 ± 9.0 |
| Hemoglobin A1c (%) (NGSP) | 5.48 ± 0.38 | 5.50 ± 0.39 | 5.48 ± 0.38 | 5.45 ± 0.38 |
| HDL cholesterol (mg/dL) | 56.8 ± 15.0 | 54.7 ± 14.0 | 56.7 ± 14.9 | 59.0 ± 16.4 |
| Low HDL cholesterol (%) | 9.2 | 10.7 | 9.2 | 8.3 |
| Triglycerides (mg/dL) | 112.0 (79.0–167.0) | 116.0 (82.0–170.0) | 112.0 (79.0–167.0) | 110.0 (76.0–166.0) |
| High triglycerides (%) | 16.8 | 18.1 | 16.8 | 16.6 |
| LDL cholesterol (mg/dL)[a] | 121.4 ± 30.9 | 122.3 ± 32.7 | 121.7 ± 30.5 | 118.7 ± 32.4 |
| High LDL cholesterol (%)[a] | 10.7 | 13.8 | 10.6 | 9.3 |
| Non-HDL cholesterol (mg/dL) | 148.1 ± 35.4 | 150.0 ± 36.6 | 148.3 ± 35.1 | 145.0 ± 36.9 |
| High non-HDL cholesterol (%) | 11.8 | 14.7 | 11.6 | 11.4 |
| Total cholesterol (mg/dL) | 204.9 ± 33.4 | 204.7 ± 35.5 | 205.0 ± 33.1 | 204.0 ± 34.3 |
| High total cholesterol (%) | 14.4 | 16.1 | 14.2 | 14.6 |
| Smoking habits | | | | |
| Non-smokers (%) | 21.9 | 25.8 | 22.2 | 17.9 |
| Past smokers (%) | 22.4 | 21.2 | 21.9 | 26.7 |
| Current smokers (%) | 55.6 | 53.0 | 55.9 | 55.4 |
| Daily alcohol consumption (g ethanol/day) | 23.0 (3.3–46.0) | 23.0 (3.3–46.0) | 23.0 (3.3–46.0) | 23.0 (3.3–46.0) |
| Daily alcohol consumption | | | | |
| Non-drinkers (%) | 14.9 | 16.1 | 14.6 | 16.6 |
| 0.1–16.5 g ethanol/day (%) | 31.0 | 33.4 | 31.8 | 23.4 |
| 16.6–46.0 g ethanol/day (%) | 41.4 | 33.2 | 41.4 | 46.0 |
| ≥46.1 g ethanol/day (%) | 12.7 | 17.3 | 12.1 | 14.0 |
| Regular leisure-time physical activity (%) | 17.5 | 13.9 | 17.4 | 19.9 |

Values are mean ± SD, median (interquartile range) or percentage (for categorical variables).
[a] Subjects with triglyceride levels ≥400 mg/dL were excluded (LDL cholesterol levels calculated using the Friedewald formula).
NGSP, National Glycohemoglobin Standardization Program; HDL, high density lipoprotein; LDL, low density lipoprotein.

to examine model fit and adherence to regression assumptions. Some dependent variables in the regression models were log-transformed to satisfy the assumption of the normality of residuals and to stabilize the variance of residuals. There were no significant interactions between sleep duration and all independent variables in all models. Evidence of multicollinearity was absent using the variance inflation factors [25]. Outliers were not detected in any model after plotting of DFBETAs [26].

## 3. Results

### 3.1. Baseline characteristics

Of the 9027 men eligible for this study between 1 April 2000 and 31 March 2001, 261 men who had missing information were excluded. Thus, the baseline subjects for analysis consisted of 8766 men. Baseline characteristics according to sleep duration are shown in Table 1. Subjects with longer sleep durations tended to have higher levels of HDL cholesterol and higher proportions of regular leisure-time physical activity, lower BMI, and lower levels of triglycerides, LDL cholesterol, and non-HDL cholesterol. Subjects with longer sleep durations tended to have a lower prevalence of low HDL cholesterol, high triglycerides, high LDL cholesterol, high non-HDL cholesterol, and high total cholesterol.

### 3.2. Incidence of low HDL cholesterol

Of the 8766 eligible men, 825 men with HDL cholesterol levels <40 mg/dL at baseline were excluded and 314 men were excluded due to attrition. Thus, the final subjects included 7627 men.

During the 37,294 person-years, there were 1022 cases of low HDL cholesterol. Table 2 summarizes baseline characteristics of the study subjects according to low HDL cholesterol status after the 6-year follow-up. The prevalence of hypertension and the proportion of current smokers were higher among those who developed low HDL cholesterol than those who did not. Subjects who developed low HDL cholesterol had lower daily alcohol consumption and regular leisure-time physical activity and a higher BMI than those who did not. Subjects who developed low HDL cholesterol had higher levels of triglycerides, LDL cholesterol, and non-HDL cholesterol, and lower levels of HDL cholesterol than those who did not.

In the Cox proportional hazards model, longer sleep duration was associated with a decreased risk of future low HDL cholesterol after adjusting for age, BMI, smoking habits (non-smokers, past smokers, and current smokers), alcohol consumption (non-drinkers, 0.1–16.5, 16.6–46.0, and ≥46.1 g ethanol/day), regular leisure-time physical activity (yes/no), and hypertension (yes/no) (Table 3).

### 3.3. Incidence of high triglycerides

Of the 8766 eligible men, 1488 men with triglyceride levels ≥200 mg/dL at baseline were excluded and 305 men were excluded due to attrition. Thus, the study subjects consisted of 6973 men.

During the 32,363 person-years, there were 1473 cases of high triglycerides. Table 2 summarizes the baseline characteristics of the study subjects according to high triglyceride status after the 6-year follow-up. The prevalence of hypertension and proportion of current smokers and heavy drinkers (≥46.1 g ethanol/day) were higher among those who developed high triglycerides than those who did not. Subjects who developed high triglycerides had a higher BMI and a lower proportion of regular physical activity than those who did not. Subjects who developed high triglycerides had higher levels of triglycerides, LDL cholesterol, non-HDL cholesterol, and total cholesterol, and lower levels of HDL cholesterol than those who did not.

In the Cox proportional hazards model adjusted for the same variables as above, subjects with a sleep duration of 5 to <7 h had a significantly lower risk of future high triglycerides than those with that of <5 h (Table 3).

**Table 2**
Baseline characteristics of study subjects according to low HDL cholesterol and high triglyceride status after 6-year follow-up.

| Baseline characteristics | Low HDL cholesterol status after follow-up ($n = 7627$)[a] | | High triglyceride status after follow-up ($n = 6973$)[b] | |
|---|---|---|---|---|
| | Normal HDL cholesterol | Low HDL cholesterol | Normal triglycerides | High triglycerides |
| *N* | 6605 | 1022 | 5500 | 1473 |
| Age (years) | 47.8 ± 4.2 | 47.7 ± 4.2 | 48.0 ± 4.3 | 47.2 ± 4.2 |
| Body mass index (kg/m$^2$) | 23.1 ± 2.8 | 24.2 ± 2.8 | 23.0 ± 2.8 | 23.8 ± 2.8 |
| Hypertension (%) | 33.8 | 36.4 | 30.7 | 36.0 |
| Fasting plasma glucose (mg/dL) | 97.7 ± 8.9 | 97.8 ± 9.0 | 97.2 ± 8.9 | 98.2 ± 8.9 |
| Hemoglobin A1c (%) (NGSP) | 5.47 ± 0.38 | 5.48 ± 0.41 | 5.46 ± 0.38 | 5.49 ± 0.39 |
| HDL cholesterol (mg/dL) | 60.9 ± 13.9 | 46.2 ± 6.2 | 60.1 ± 15.2 | 54.0 ± 12.7 |
| Triglycerides (mg/dL) | 103.0 (74.0–149.0) | 135.0 (99.0–191.3) | 90.0 (69.0–119.0) | 141.0 (113.0–169.0) |
| LDL cholesterol (mg/dL)[c] | 120.5 ± 30.5 | 126.9 ± 31.6 | 120.7 ± 29.4 | 127.9 ± 32.6 |
| Non-HDL cholesterol (mg/dL) | 144.8 ± 34.3 | 157.6 ± 34.0 | 140.0 ± 31.9 | 155.8 ± 34.2 |
| Total cholesterol (mg/dL) | 205.7 ± 32.6 | 203.8 ± 33.0 | 200.1 ± 31.2 | 209.8 ± 32.5 |
| Smoking habits | | | | |
| Non-smokers (%) | 23.6 | 16.7 | 24.8 | 17.5 |
| Past smokers (%) | 24.0 | 19.0 | 23.9 | 20.2 |
| Current smokers (%) | 52.4 | 64.3 | 51.3 | 62.3 |
| Daily alcohol consumption (g ethanol/day) | 23.0 (8.2–46.0) | 16.4 (1.6–32.9) | 23.0 (3.3–46.0) | 24.6 (4.9–46.0) |
| Daily alcohol consumption | | | | |
| Non-drinkers (%) | 12.6 | 20.7 | 16.2 | 14.1 |
| 0.1–16.5 g ethanol/day (%) | 29.2 | 37.9 | 33.3 | 25.7 |
| 16.6–46.0 g ethanol/day (%) | 44.5 | 30.6 | 41.0 | 42.3 |
| ≥46.1 g ethanol/day (%) | 13.7 | 10.8 | 9.6 | 17.9 |
| Regular leisure-time physical activity (%) | 18.7 | 13.4 | 19.2 | 15.2 |

Values are mean ± SD, median (interquartile range) or percentage (for categorical variables).
[a] Of the 8766 eligible men in Table 1, 825 men with HDL cholesterol level <40 mg/dL were excluded at baseline and 314 men were excluded due to attrition.
[b] Of the 8766 eligible men in Table 1, 1488 men with triglyceride level ≥200 mg/dL were excluded at baseline and 305 men were excluded due to attrition.
[c] Subjects with triglyceride levels ≥400 mg/dL were excluded (LDL cholesterol levels calculated using the Friedewald formula).
HDL, high density lipoprotein; NGSP, National Glycohemoglobin Standardization Program; LDL, low density lipoprotein.

### *3.4. Incidence of high LDL cholesterol, high non-HDL cholesterol, and high total cholesterol*

For high LDL cholesterol, of the 8766 eligible men the following were excluded: 246 men with triglyceride levels ≥400 mg/dL at baselined, 924 men with LDL cholesterol levels ≥160 mg/dL at baseline, 304 men due to attrition, and 19 men with triglyceride levels ≥400 mg/dL at all follow-up examinations. Thus, the study subjects consisted of 7273 men. During the 34,570 person-years, there were 1307 cases of high LDL cholesterol.

For high non-HDL cholesterol, of the 8766 eligible men, 1042 men with non-HDL cholesterol levels ≥190 mg/dL at baseline were excluded as were 309 men due to attrition. Thus, the study subjects consisted of 7415 men. During the 35,327 person-years, there were 1301 cases of high non-HDL cholesterol.

For high total cholesterol, of the 8766 eligible men, 1269 men with total cholesterol levels ≥240 mg/dL at baseline were excluded as were 301 men due to attrition. Thus, the study subjects consisted of 7196 men. During the 33,864 person-years, there were 1462 cases of high total cholesterol.

**Table 3**
Multiple-adjusted hazard ratios of lipid profile abnormalities in relation to sleep duration.

| Sleep duration (h) | Case | Person-years | Incidence rate (per 1000 person-years) | Crude model | Multiple-adjusted model[a] |
|---|---|---|---|---|---|
| Low HDL cholesterol ($n = 7627$) | | | | | |
| <5 | 96 | 2540 | 37.8 | 1.00 | 1.00 |
| 5 to <7 | 840 | 30,315 | 27.7 | 0.74 (0.60–0.91) | 0.79 (0.64–0.97) |
| ≥7 | 86 | 4439 | 19.4 | 0.52 (0.39–0.70) | 0.62 (0.46–0.83) |
| High triglycerides ($n = 6973$) | | | | | |
| <5 | 130 | 2182 | 59.6 | 1.00 | 1.00 |
| 5 to <7 | 1167 | 26,460 | 44.1 | 0.74 (0.62–0.89) | 0.81 (0.68–0.98) |
| ≥7 | 176 | 3721 | 47.3 | 0.80 (0.64–1.00) | 0.90 (0.71–1.13) |
| High LDL cholesterol ($n = 7273$) | | | | | |
| <5 | 90 | 2374 | 37.9 | 1.00 | 1.00 |
| 5 to <7 | 1067 | 28,146 | 37.9 | 1.00 (0.80–1.23) | 1.03 (0.83–1.28) |
| ≥7 | 150 | 4050 | 37.0 | 0.97 (0.75–1.26) | 1.08 (0.83–1.40) |
| High non-HDL cholesterol ($n = 7415$) | | | | | |
| <5 | 100 | 2444 | 40.9 | 1.00 | 1.00 |
| 5 to <7 | 1067 | 28,758 | 37.1 | 0.90 (0.74–1.11) | 0.95 (0.77–1.17) |
| ≥7 | 134 | 4125 | 32.5 | 0.79 (0.61–1.03) | 0.90 (0.69–1.17) |
| High total cholesterol ($n = 7196$) | | | | | |
| <5 | 101 | 2383 | 42.4 | 1.00 | 1.00 |
| 5 to <7 | 1191 | 27,593 | 43.2 | 1.01 (0.83–1.24) | 1.04 (0.85–1.27) |
| ≥7 | 170 | 3888 | 43.7 | 1.02 (0.80–1.30) | 1.08 (0.84–1.38) |

Model data are hazard ratios (95% confidence intervals).
[a] Adjusted for age, body mass index, smoking habits (non-smokers, past smokers and current smokers), alcohol consumption (non-drinkers, 0.1–16.5, 16.6–46.0, and ≥46.1 g ethanol/day), regular leisure-time physical activity (yes/no), and hypertension (yes/no).
HDL, high density lipoprotein; LDL, low density lipoprotein.

In the Cox proportional hazards model adjusted for the same variables as above, sleep duration was not associated with the risk of future high LDL cholesterol, high non-HDL cholesterol, or high total cholesterol (Table 3).

In this study, taking oral lipid-lowering medications was not included in the study outcome criteria for each lipid profile abnormality since we could not determine for which lipid profile abnormalities oral lipid-lowering medications were taken. We reanalyzed the association between sleep duration and the risk of each lipid profile abnormality after excluding subjects who were taking oral lipid-lowering medications during the follow-up period, and similar results were obtained (data not shown).

### 3.5. Association between sleep duration and future HDL cholesterol, triglycerides, LDL cholesterol, non-HDL cholesterol, and total cholesterol as continuous outcomes

The association between sleep duration and future lipid measurements was examined as continuous outcomes using multiple linear regression analysis. Of the eligible 7627, 6973, 7273, 7415, and 7196 men for the analyses using Cox proportional hazards models of low HDL cholesterol, high triglycerides, high LDL cholesterol, high non-HDL cholesterol, and high total cholesterol, respectively, we included subjects with lipid profile measurements at the sixth examination who had not taken oral lipid-lowering medications during the follow-up period in the multiple linear regression analysis. Thus, the final study subjects consisted of 6199, 6199, 5941, 6199, and 6200 subjects for low HDL cholesterol, high triglycerides, high LDL cholesterol, high non-HDL cholesterol, and high total cholesterol, respectively. Almost identical results to those observed in the initial version were obtained using Cox proportional hazards models. Regarding the association between sleep duration and future non-HDL cholesterol, in the Cox model, longer sleep duration had a tendency toward a decreased odds of non-HDL cholesterol but this was not significant (Table 3). However, when using the multiple linear regression model, this association was significant (Table 4). We think that it was due to sample power differences between the Cox model and the multiple linear regression model.

**Table 4**
Multiple linear regression analysis of lipid profiles in relation to sleep duration.

| Sleep duration (h) | β | β′ (95% CI) | *P*-value |
|---|---|---|---|
| $Log_e$ HDL cholesterol[a] ($n = 6199$) | | | |
| <5 | Reference | Reference | |
| 5 to <7 | 0.023 | 0.037 (0.00 to 0.04) | 0.038 |
| ≥7 | 0.035 | 0.046 (0.01 to 0.06) | 0.009 |
| $Log_e$ triglycerides[a] ($n = 6199$) | | | |
| <5 | Reference | Reference | |
| 5 to <7 | −0.052 | −0.037 (−0.10 to 0.00) | 0.049 |
| ≥7 | −0.049 | −0.028 (−0.11 to 0.01) | 0.133 |
| LDL cholesterol[b] ($n = 5941$) | | | |
| <5 | Reference | Reference | |
| 5 to <7 | −2.457 | −0.032 (−5.40 to −0.49) | 0.102 |
| ≥7 | −2.879 | −0.031 (−6.47 to 0.71) | 0.116 |
| Non-HDL cholesterol[a] ($n = 6199$) | | | |
| <5 | Reference | Reference | |
| 5 to <7 | −3.523 | −0.041 (−6.70 to −0.35) | 0.030 |
| ≥7 | −4.226 | −0.041 (−8.01 to −0.35) | 0.032 |
| Total cholesterol[b] ($n = 6200$) | | | |
| <5 | Reference | Reference | |
| 5 to <7 | −2.217 | −0.027 (−5.36 to 0.92) | 0.166 |
| ≥7 | −2.026 | −0.020 (−5.86 to 1.80) | 0.300 |

$Log_e$ denotes natural logarithm.
β and β′ denote regression coefficient and standardized regression coefficient, respectively.
[a] Adjusted for age, body mass index, smoking habits (non-smokers, past smokers and current smokers), alcohol consumption (non-drinkers, 0.1–16.5, 16.6–46.0, and ≥46.1 g ethanol/day), regular leisure-time physical activity (yes/no), and hypertension (yes/no).
[b] Adjusted for age, body mass index, $log_e$ body mass index, smoking habits (non-smokers, past smokers and current smokers), alcohol consumption (non-drinkers, 0.1–16.5, 16.6–46.0, and ≥46.1 g ethanol/day), regular leisure-time physical activity (yes/no), and hypertension (yes/no).
CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein.

## 4. Discussion

These prospective data demonstrated that moderate and/or long sleep durations were associated with a decreased risk of future low HDL cholesterol and high triglycerides. These associations were independent of age, BMI, smoking habits, alcohol consumption, regular leisure-time physical activity, and hypertension. However, no associations were revealed between sleep duration and risk of future high LDL cholesterol, non-HDL cholesterol, or total cholesterol.

Although a few cross-sectional studies have examined the association between sleep duration and dyslipidemia, the results of these studies were inconclusive [10–13]. These previous epidemiological studies cannot be used to draw conclusions on the cause-and-effect relationship because of the cross-sectional nature of these data. Only two prospective studies examined the association between sleep duration and each lipid profile abnormality or hypercholesterolemia [14,15]. Ruiter Petrov et al. [14] reported that longer sleep duration was associated with increased future total cholesterol, triglycerides, and LDL levels, but not HDL. In our study, moderate and/or long sleep durations were associated with a decreased risk of future low HDL cholesterol and high triglycerides. The age distribution of study subjects and ethnicity differences might explain these different results. Gangwisch et al. [15] showed that longer sleep duration in adolescent women, but not men, was associated with a decreased odds of future high cholesterol. However, in their study, all study subjects were adolescents (grades 7–12 at baseline), the determination of hypercholesterolemia was based on subjects' self-report questionnaires, and they did not examine the association between sleep duration and risk of each lipid profile abnormality.

In our prospective study, sleep duration of 5 to <7 h was associated with a significantly decreased risk of future high triglycerides than <5 h, and ≥7 h tended to be associated with a decreased risk of future high triglycerides but this association was not significant. If sleep duration had been categorized further in our study, we may have been able to clarify the association between longer sleep duration and the risk of future high triglycerides. To confirm this, further research on this association is needed.

Although we did not identify why longer sleep duration decreases the risk of future low HDL and triglyceride levels, insulin resistance may be a plausible partial mechanism. Broussard et al. [27] reported that sleep restriction reduced insulin sensitivity in 17 healthy adults in a randomized 4-day crossover clinical study of either 4.5 or 8.5 h in bed under controlled caloric intake and physical activity conditions. Furthermore, in an insulin-resistant state, high triglycerides occur as a function of increased production of very low-density cholesterol (VLDL), which is a triglyceride-rich lipoprotein, and of intestinally derived lipoprotein. Low HDL cholesterol occurs as a function of decreased production of HDL cholesterol as a degradation product of VLDL as a result of the reduced lipoprotein lipase activity, and as a function of the production of HDL-depleted cholesteryl ester by the action of cholesteryl ester transfer protein [28]. Therefore, shorter sleep duration might result in insulin resistance, which leads to low HDL cholesterol and high triglyceride levels. On the other hand, in our study, sleep duration was not associated with future risk of high total cholesterol or LDL cholesterol.

In previous cross-sectional and prospective studies, it has been reported that insulin resistance was not associated with high total cholesterol or LDL cholesterol [29,30]. That is, in part, why sleep duration was not associated with future risk of high total cholesterol or high LDL cholesterol. In our study, the association between sleep duration and the risk of future high non-HDL cholesterol was not stronger than the association between sleep duration and the risk of future high triglycerides. That is why non-HDL cholesterol includes both triglyceride-rich lipoprotein (VLDL, IDL) and triglyceride-non-rich lipoprotein (LDL), and why insulin resistance has been reported to be associated with triglycerides, but not with LDL [29,30]. The role of sleep duration in the pathogenesis of lipid profile abnormalities requires further investigation.

There were some limitations in our study. First, information regarding sleep duration was acquired by self-report measures, which produced a reasonable measure of actual sleep duration. A previous study demonstrated a good correlation between self-reported sleep duration and sleep duration as measured through actigraphic monitoring [31]. However, some studies have indicated that self-reported sleep duration tends to be longer than when measured through actigraphic [32] and polysomnographic [33] monitoring. Second, the question on sleep duration asked about average sleep duration per week, and thus we could not distinguish between weeknights and weekend nights. Third, our analysis was adjusted for multiple potential confounding variables, including age, BMI, smoking habits, alcohol consumption, regular leisure-time physical activity, and hypertension. However, other unknown or unmeasured confounding variables, such as the quality of sleep and stress, might explain the relationship between sleep duration and lipid profile abnormalities. Fourth, the population of the current study was limited to middle-aged Japanese men, so it is unclear whether we can generalize our findings to women, older men, or other ethnic groups. Finally, as we only used three levels to define the sleep duration variable, other classifications of sleep duration might be more appropriate.

In conclusion, longer sleep duration was significantly associated with a decreased risk of future low HDL cholesterol and high triglycerides. Our results suggest the possibility that the increasing length of sleep might prevent future low HDL cholesterol and high triglycerides. The quantity of sleep might play a key role in the risk of future lipid profile abnormalities. To confirm this, further research on these associations is necessary.

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## Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.06.011.

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